IN THE U.S.PATENT AND TRADEMARK OFFICE

Applicant: BIOSPECTRUM, INC.
Serial No.: 10/579,163 Art Unit: 1612
Filed: May 11, 2006 Examiners: KISHORE, GOLLAMUDIS
For: Multiple Layered Liposome and Preparation Method Thereof

DECLARATION UNDER 37 C.F.R. SECTION 1.132

Honorable Comissioner of
Patent and Trademarks
Washington, D.C. 20231

I, Deokhoon Park, a citizen of Korea, residing at Samsung First Apt. Pungdeokchun 1-Dong, Kyunggi-Do 449-762, Korea, hereby declares as follows:

1. I am an inventor of the subject matter of the above identified application.

2. My personal particulars are summarized as follows:

[Deokhoon Park]
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[Education]
BS – Dept. of Agriculture, KyungPook National University (1987)
MS – Dept. of Agriculture, KyungPook National University (1989)
PhD – Dept. of Agriculture, KyungPook National University (1992)

[Research Interests]
Preparation of liposome
Preparation of cosmetic compositions
Development of functional ingredients

[Papers]
1. Synthesis of an artificial gene for the Shorthorn sculpin antifreeze protein and its introduction into tobacco plants. Mol. Cells. Vol. 1. pp. 261-266 (1991)

2. A brassica cDNA clone encoding a bifunctional hydroxyl methylmethylpyrimidine kinase/ thamine-phosphate pyrophosphorylase involved in thiamin Biosynthesis. Plant Mol. Biol. 37, pp. 955-966 (1998)

3. Control of Circadian Rhythms and photoperiodic flowering by the Arabidopsis Gigantea gene. SCIENCE 285, pp. 1449-1628 (1999)

4. Expression of a functional human-cytosolic Cu/Zn superoxide dismutase in transgenic tobacco. BioTechnology Letters 24: pp. 681-686 (2002). ***corresponding author**

5. In vitro antibacterial and anti-inflammatory activities of Honokiol and Magnolol against Propionibacterium sp. Eur. J. Pharmacol. 496 (2004), 189-195. ***corresponding author**

6.Evaluation of the anti-inflammatory and atopic dermatitis-mitigating effects of BSASM, a multiherbal preparation. J. Ethnopharmacol. 1, 2005. ***corresponding author**

7. Anti-inflammatory effects of magnolol and honokiol are mediated through inhibition of downstream pathway of the MEKK-1 in NF-κB activation signaling. Planta medica 2005:71:338-343. ***corresponding author**

8. Glycyrrhizin(GR) induces melanogenesis through elevating a cAMP level in B16 melanoma cells. J. I. D. 2005: 124(2) 405-411. ***corresponding author**

9. Transdermal delivery of interferon gamma (IFN-gamma) mediated by penetratin, a cell-permeable peptide. Biotechnology and applied Biochemistry, 2005, 42(2), 169-173. ***corresponding author**

10. Asiaticoside induces Human Collagen I Synthesis through TGF-beta receptor I kinase (TbetaRI kinase) -independent Smad signaling. Planta Medica. 2006, 72, 324-328. ***corresponding author**

11. Anti-inflammatory and atopic dermatitis-mitigating effects of BSASM, a multiherbal preparation. Recent Progress in Medicinal Plants. Jan 2006, 12, 221-237. Review.

12. Rosmarinic acid (RA) as a downstream inhibitor of IKK bata in TNF alpha–induced upregulation of CCL11 & CCR-3. British Journal of Pharmacology 2006, Jun;148(3):366-75. ***corresponding author**

13. Emodin inhibits TNF alpha-induced MMP-1 expression through suppression of JNK and p42/44MAPK. Life Sciences. 200679(26):2480-5. ***corresponding author**

14. Panax ginseng induces human Type I collagen synthesis through activation of Smad signaling. J. Ethnopharmacol. 2006, 109:29-34. ***corresponding author**

15. Involvement of nuclear factor-kapaB in the inhibition of pro-inflammatory mediators by pinosylvin. Planta Med. 2006 Jul;72(9):801-6. ***corresponding author**

16. A cell-based assay system for high-throughput screening of anti-wrinkle agents in human dermal fibroblast transfectant cells. Biotechnol Appl Biochem. 2007;47(Pt 1):27-31.***corresponding author**

17. Effect of Camellia japonica oil on human type I procollagen production and skin barrier function. J Ethnopharmacol. 2007;112(1):127-31. ***corresponding author**

18. Rosmarinic acid induces melanogenesis through protein kinase A activation signaling. Biochem Pharmacol. 2007 Oct 1;74(7):960-968.***corresponding author**

19. Mechanisms of melanogenesis inhibition by 2,5-dimethyl-4-hydroxy- 3(2H)-furanone. Br J Dermatol. 2007 Aug;157(2):242-8. ***corresponding author**

20. Diosgenin inhibits melanogenesis through the activation of phosphatidylinositol-3-kinase pathway (PI3K) signaling. Life Sci. 2007 Jun 27;81(3):249-54. ***corresponding author**

21. Mechanisms of depigmentation by alpha-bisabolol. J Dermatol Sci. 2008 Dec;52(3):219-22. Epub 2008 Aug 8. ***corresponding author**

22. Evaluation of the effects of a preparation containing asiaticoside on periocular wrinkles of human volunteers.Int J Cosmet Sci. 2008 Jun;30(3):167-73 ***corresponding author**

23. Mechanisms of carvacrol-induced expression of type I collagen gene.J Dermatol Sci. 2008 Dec;52(3):160-9. Epub 2008 Aug 12. ***corresponding author**

[Granted Patents]

1. Nano liposome composition(KR0603814)
2. Multiple layered liposome and preparation methodthereof(KR0461458)
3. Expression vector with Penetratin as a fusion partnerto enhance transdermal delivery of recombinant proteins(KR0729830)
4. Cosmetic composition comprising asiaticoside(KR0511944)
5. Cosmetic composition for reducing skin wrinklescomprisings

asiaticoside(KR0641302)

6. Composition for improving atopic dermatitis comprisingmagnolol and honokiol(KR0699538)

7. Cosmetic composition for improving skin wrinklecomprising extract from Hypochoeris radicata L(KR0702461)

8. Antimicrobial composition comprising natural plantextract(KR0729831)

9. Composition for improving wrinkle on skin comprising ethanol extract of Aralia elata as an efficient ingredient(KR0829832)

10. Antinflammatory composition comprising natural plantextract(KR1009904)

11. Preparation methods of Panax ginseng extract increased contents of physiologically active substances Rb1, Rb2, Rc and Rd(KR0762965)

12. Naturotics(KR0782599)

13. Reverse-Phase Multi-Lamella Vesicle Capturing AqueousPhysiologically Active Ingredients(KR0831627)

14. Skin care composition comprising the extract ofCentella asiatica and Magnolia kobus(KR0795512)

15. Composition for ameliorating inflammation comprisingpinosylvin and rosmarinic acid(KR0795513)

16. Composition for skin whitening containing diosgenin(KR0795514)

17. A skin whitening compositions comprising natural plantextract(KR0829831)

18. Cosmetic compositions for anti-aging of skin comprisingdiosgenin and dioscin(KR0782600)

19. Compositions comprising compounds of natural origin for damaged skin(KR0812596)

20. Composition for skin whitening comprising artemisinine(KR0795515)

21. A Composition for Improving Wrinkle on Skin Comprising Plant Extracts(KR0729832)

22. A Composition for Improving Wrinkle on Skin Comprising Plant Extracts(KR0729833)

23. Biphenyl Diol Derivatives and Compositions Comprising the Same as an Active Ingredient(KR0892596)

24. Compositions for Ameliorating Symptom of Atopic Dermatitis(KR0832332)

25. Agents for Improving Skin Wrinkles Comprising Carvacrol as an Active Ingredient(KR0893162)

26. Compositions for Improving Skin Conditions Comprising α-Bisabolol as an Active Ingredient(KR0823533)

27. Agents for Skin Whitening Comprising Barbituric acid as an Active Ingredient(KR0862969)

28. Composition for skin external application comprising rosmarinic acid for preventing or treating rosacea(KR0934691)

29. Composition for skin whitening or promoting hair growth comprising gypenoside(KR0886743)

30. Compositions for Improving Skin Wrinkle Comprising Piperine as an Active Ingredient(KR0843125)
31. Compositions for Improving Skin Wrinkle Comprising Hyperin as an Active Ingredient(KR0862957)
32. Compositions for Improving Skin Conditions Comprising Breu branco essential oil as an Active Ingredient(KR0845888)
33. Compositions for Improving Skin Conditions Comprising Crowberry extract(KR0863614)
34. Skincare composition containing priprioca oil(KR0863615)
35. Skincare composition containing Brazilian pepper oil(KR0848800)
36. Skincare composition containing copaiba balsam oil(KR0863616)
37. Compositions for Improving Skin Conditions Comprising Alum(KR0863617)
38. Compositions for Improving Skin Conditions Comprising protocatechuic acid(KR0863618)
39. Composition containing S-(-)-tulipalinB or Acetylated-S-(-)-tulipalinB(KR0808490)
40. Agents for Preventing Hair Loss Comprising Delphinidin as an Active Ingredient(KR0902768)
41. Agents for Improving Skin Whitening Comprising Isorhamnetin as an Active Ingredient(KR0902769)
42. Multi-Emulsified Vesicles Comprising a Multi Lamellar Liposome and Phospholipid Monolayer Nanoliposomes(KR0921959)
43. Agents for Improving Wrinkles on Skin Comprising Alpha-pinene as an Active Ingredient(KR0873946)
44. Compositions for Improving Skin Wrinkle Comprising Arctigenin as an Active Ingredient(KR0901661)
45. Compositions for Improving Skin Conditions Comprising Citral as an Active Ingredient(KR0878586)
46. Compositions for Improving Skin Conditions Comprising Isomenthone as an Active Ingredient(KR0919897)
47. composition for melanin induction containing purine derivatives(KR0924060)
48. Composition for inducing hair growth containing Boehmeria sieboldiana Bl. extract or apigenin(KR0957577)
49. Agents for skin whitening containing Platycodin D(KR0901519)
50. Compositions for Stimulating Hair Growth Comprising α-Bisabolol as an Active Ingredient(KR0823535)
51. Compositions for Anti-obesity Comprising α-Bisabolol as an Active Ingredient(KR0823537)
52. Compositions for Anti-Obesity Comprising Matrine or Its Oxidized Derivatives(KR0862967)
53. Compositions for inhibiting losses of hair comprising protocatechuic acid(KR0921251)
54. Anti-obesity Agents Comprising Carvacrol as an Active Ingredient(KR0919898)

55. Skin Whitening Agents Comprising Matrine or Its Oxidized Derivatives(KR0879244)
56. Cosmetic compostions comprising andiroba oils(KR1044597)
57. Multiple Layered Liposome and Preparation Method Thereof(JP4758915)
58. Compositions Comprising Compounds of Natural Origin for Damaged Skin(US7,994,141)

3. I am thoroughly familiar with the Office Action dated May 13, 2011, wherein claims 3, 6, 7 and 12 of the present application have been rejected under 35 U.S.C. 103(a) as being unpatentable over Popp(US2006/0029657) in combination with Foldvari (USPN 5,853,755).

In the Office Action, the Examiner concluded that the invention as a whole would have been obvious to a person having ordinary skill in the art at the time the invention was made, as evidenced by the references, specifically in the absence of evidence to the contrary. In this regard, I have conducted preparation of skin protectant compositions of Popp according to Example 1 of Popp.

4. Under my direction and control, the preparation of skin protectant compositions was conducted for determining that a multilayered liposome cannot be prepared by the method as disclosed in Popp using a non high-pressure homogenizer regardless of a fatty acid as an oil component.

(1) Preparation Method

Example 1 of Popp was made exactly in accordance with the description as description in Popp. The Components and ratio thereof are shown in the following Table 1:

Table 1.

Component	% W/W	
	Sample 1	Sample 2
Caprylic/Capric triglyceride	22.4	22.4
Glycerin	8.75	8.75
Pentylene Glycol	4.75	4.75
Coconut oil	3.5	3.5
Hydrogenated Lecithin	1.5	1.5
Shea Butter	1.35	1.35
Hydroxyethylcellulose	0.35	0.35
Squalene	0.25	0.25
Carbomer	0.1	0.1
Sodium Carbomer	0.1	0.1
Xanthan Gum	0.1	0.1

Ceramide 3	0.0025	0.0025
Stearic acid (fatty acid)	0	1
Water	56.8475	55.8475

Compositions of Popp were prepared according to Example 1 of Popp as follows. An aqueous phase is prepared by mixing the pentylene glycol, glycerin, and purified water. The hydroxyethylcellulose is then added with slow homogenizing. This mixture is then stirred fast for about 20 minutes while heating to a temperature of 60°C The aqueous phase is then cooled to a temperature of 40°C, and homogenized while cooling.

An oil phase is prepared by mixing the Caprylic/Capric Triglyceride, Squalane, Shea Butter, Coconut Oil, and Xanthan Gum (and stearic acid for sample 2) while heating to a temperature of 42°C. The Carbomer and Sodium Carbomer are then added under slow homogenization until dispersed, and the mixture is then heated to 42°C.

While stirring, the aqueous phase is quickly added to the oil phase under vacuum. This mixture is stirred fast and recirculated for about 35 minutes, while maintaining the temperature at 40°C. The mixture is then cooled to about 30°C while maintain the stirring at a maximum 45 rpm. The Ceramide 3 and the Hydrogenated Lecithin are then added to the emulsion while stirring at about 30 rpm. While stirring at about 30 rpm, the emulsion is homogenized at about 3000 rpm for about 55 minutes at a temperature of not more than 34°C. The emulsion is cooled to 25°C while stirring at about 30 rpm.

(2) Test Method

The size of the prepared compositions was measured. The size of emulsified particles was measured three times for each sample using a particle size analyzer (model 370, Nicomp, USA). Mean values of the measured results and the results obtained by 600X microscopic observation are provided in Table 2, Figure 1 and 2, below.

(3) Test Results

The test results of the compositions prepared by Example 1 of Popp are shown in Table 2, Figure 1 and 2, below.

Table 2

	Sample 1	Sample 2
Particle size distribution	600-1500	600-1500
Mean particle size (nm)	1000	1000
Structure of Liposomes	Unilamellar	Unilamellar

Fig.1 [Sample 1]

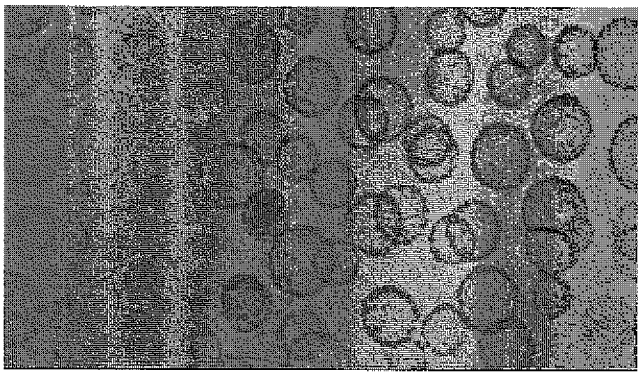
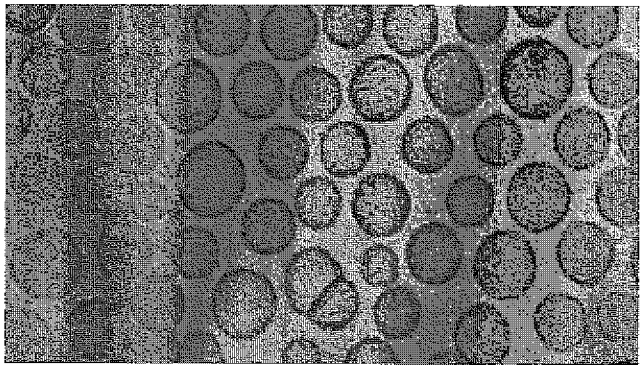


Fig.2 [Sample 2]



As shown in Table 2, the Compositions prepared by the method according to Example 1 of Popp had 1,000 nm mean particle size. In addition, as shown in Fig. 1 and 2, the compositions were not multilayered liposomes but unilamellar liposomes.

5. Conclusion

As shown in the results, it is proven that a multilayered liposome cannot be prepared by the method according to Example 1 of Popp without using a high-pressure homogenizer. In addition, it is also proven that the multilayered liposome cannot be prepared by the method, which uses oil components as disclosed in Popp plus a fatty acid, according to Example 1 of Popp using a non high-pressure homogenizer.

In contrast, the present invention can prepare the multilayered liposomes, which are highly uniform in both shape and size, without using a high-pressure homogenizer. Therefore, it is apparent that Popp does not teach the present invention.

6. I hereby declare that all statements made herein are to my best knowledge and are believed to be true; further these statements were made with the knowledge that willful

false statements are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issuing therefrom.

Dated: 2nd day of September 2011

Signature: 

Deokhoon Park